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NEUROTRANSMITTERS AND RESTING STATE NETWORKS: CLINICAL IMPLICATION FOR MAJOR PSYCHIATRIC DISORDER

Neurotrasmettitori e Resting State Networks: implicazioni cliniche nei Disturbi Psichiatrici Maggiori

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SUMMARY

BACKGROUND

Introduction

In recent years, several neurobiological alterations have been found in major psychiatric disorders[1, 2]. In particular, neuroimaging works have detected changes in the functional architecture of brain intrinsic activity in patients affected by disorders like bipolar disorder (BD) and schizophrenia (e.g.,[1, 2]).

This PhD thesis, published on Molecular Psychiatry[3], investigates the relationships between resting-state networks (RSNs) and neurotransmitters and their implications for major psychiatric disorders.

Resting-state functional magnetic resonance imaging (fMRI) studies have demonstrated that different subcortical and cortical brain regions are organized in functionally connected large-scale RSNs - e.g., sensorimotor network (SMN), default-mode network (DMN), salience network (SN), central executive network (CEN) and auditory and visual networks[4-16].

The functional organization and intrinsic activity of such RSNs, as well as their relationship and interaction, have shown a number of alterations in various psychiatric disorders.

In this context, a disbalance between SMN and DMN has been detected in BD[17], while complex changes in the relationships between DMN, CEN, SN and sensory networks have been observed in schizophrenia, suggesting that different patterns of functional re-organization in brain intrinsic activity may underpin distinct psychopathological states[18-22].

One question that arises is which potential mechanisms could lead or contribute to the functional re-organization or disorganization of RSNs and their intrinsic activity – this remains unclear though.

Independently, an involvement of neurotransmitters in the pathophysiology of mental illnesses has been supposed since the introduction of psychopharmacological treatments and a better understanding of their pharmacodynamics[23].

In particular, during the 1970s, the dopamine (DA) hypothesis of schizophrenia has been conceptualized, when the antipsychotic and antimanic effects of DA receptor blockade agents suggested that psychotic and manic symptoms are related to a dysregulation of dopaminergic activity[24]. According to this hypothesis, the etiology of schizophrenia was traced to excessive transmission at DA receptors[25].

The model has been revised by Kapur and re-conceptualized by combining subcortical hyper-dopaminergia with prefrontal hypo-dopaminergia, which behaviorally results in the attribution of aberrant salience to stimuli[25].

On the other hand, mood effects of molecules which modify the serotonin (5-HT) metabolism suggested an involvement of monoaminergic dysregulation in affective symptomatology[26].

During the mid-1960s, this evidence gave rise to the monoamine theory of affective disorders, which assumed a relationship between depression and decreased levels of centrally available neurotransmitters[27].

Taken together, changes in neurotransmitters activity, as well as in sensitization of their receptors, have been associated with schizophrenia and affective disorders[28-32].

Considering the co-occurrence of alterations in the neurotransmitter systems and RSNs in such psychiatric disorders, a link between these chemical and functional abnormalities could be supposed.

The exact mechanisms of neurotransmitters on especially the circuitry or network level of brain activity remain largely unclear though. However, the widespread projections of these brainstem neurotransmitters nuclei to several subcortical and cortical areas suggest

an impact of neurotransmitters activity, beyond specific local regions, on the global functional architecture of brain activity and its RSNs.

This is supported by recent imaging studies investigating the effects of pharmacological DA or 5-HT challenge on RSNs whose results will be reviewed here.

Resting-state networks

Coherent neuronal oscillations across distributed brain areas in the low-frequency range (<0.1Hz) consistently organize the RSNs, including the SMN, DMN and SN[6-12, 14, 33-36].

The SMN – which comprises the middle cingulate cortex (MCC), dorsal striatum, ventral nuclei of thalamus and postcentral gyrus, precentral gyrus, premotor and supplemental motor areas (SMA) – is involved in sensory processing and motor functions[9, 37].

The DMN - which mainly concerns cortical midline regions, such as the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), along with parietotemporal multimodal association cortices - is involved in ideation, internal thought and mind wandering[7, 38-40].

The SN - which includes the supragenual ACC (SACC), amygdala, nucleus accumbens (NAc), dorsomedial thalamus, insula and ventrolateral prefrontal cortex (VLPFC) – is involved in salience attribution, interoceptive awareness, and reward system[8, 13, 41, 42].

The activity of each RSN is not isolated, they have complex interactions - that concern the topographical patterns in signal power and variance across brain regions - and that could be positive (i.e., correlate) or negative (i.e., anticorrelate)[9, 43].

Moreover, RSNs are frequently organized in balances, for example the DMN, which is involved in internal thought, is related to psychomotor behavior through its anticorrelated relationship with the SMN[9].

Neurotransmitters systems

The dopaminergic mesencephalic system is mainly composed of the substantia nigra pars compacta (SNc), which gives rise to the nigrostriatal pathway, and the ventral tegmental area (VTA), which gives rise to the mesocorticolimbic pathway[44].

The SNc projects mainly to the dorsal striatum, including dorsolateral portions of the caudate and putamen, in addition to the globus pallidus, subthalamic nucleus, and ventral thalamic nuclei[44, 45].

Dopaminergic projections modulate neuronal activity in these dorsal parts of striatopallidal regions by acting on excitatory D1 receptors, mainly located in the excitatory direct pathway, and inhibitory D2 receptors, mainly located in the inhibitory indirect pathway[44]. Moreover, DA neurons project diffusely to the cortex mainly via D1 signaling, where motor areas (in particular premotor and SMA) display greater innervation than sensory areas[44].

Optogenetic stimulation of the dopaminergic neurons of SNc was shown to facilitate motor activity (e.g.,[46]). Thus, the resulting effect of DA activity is a facilitation of goal-directed movements[44, 47].

The VTA projects to the medial PFC - including the medial orbitofrontal cortex (OFC) and ACC - ventral striatum - including the NAc and the ventral parts of caudate and putamen - and dorsomedial thalamus[44, 48].

In particular, ACC mainly expresses D1 receptors, the ventral parts of striatopallidal regions mainly expresses D2-like receptors, while dorsomedial thalamus mainly expresses D1 and D3 receptors[44].

The resulting effects of DA activity favor motivation and reward-related behaviors, as well as cognitive functions such as attention and working memory[44, 49, 50].

The serotonergic raphe nuclei (RNi) project to the striatum and thalamus (including the posterior complex and lateral geniculate nuclei, the ventral anterior and ventrolateral nuclei, and the dorsomedial nucleus), as well as the cingulate cortex, PFC (including medial OFC), temporal and sensory cortices[51-55].

In particular, the basal ganglia regions express 5-HT2A receptors, mainly in the dorsal striatum, as well as 5-HT1B, 5-HT4 and 5-HT6 receptors, mainly in the ventral striatum[51]; the thalamic regions express 5-HT1A and 5-HT2 receptors (mainly in the ventral nuclei), 5-HT2C receptors (mainly in the geniculate complexes) and 5-HT7 receptors (mainly in the dorsomedial nucleus)[51, 52]; prefrontal and cingulate cortex mainly express 5-HT1A, and 5-HT1B receptors, as well as 5-HT2A and 5-HT2C receptors[51], while motor and sensory cortices (i.e., somatosensory, auditory and visual areas), which are densely innervated by serotonergic projections, mainly express 5-HT1 receptors[52, 56-58].

Optogenetic stimulation of the serotonergic neurons of RNi resulted in inhibition of sensory responsivity (gating sensory-driven responses), delayed responses, patience or waiting behavior, and slower motor activity[59-64].

Thus, the resulting effect of 5-HT activity is a modulation of sensory processing along with inhibition of motor functions and impulsive behaviors[52, 65]. See **Supplemental Figure 1**.

Connectivity pattern between neurotransmitter nuclei and resting-state networks

To date, only few studies have explored the relationships of brainstem neurotransmitters synthesizing centers with the various regions of RSNs and their activity[66].

Considering the anatomical connections, the dopaminergic nigrostriatal pathway mainly projects thus to regions of the SMN (e.g., dorsal striatum, globus pallidus, and ventral thalamic nuclei); while the mesocorticolimbic pathway mainly projects to regions of the SN (e.g., SACC, NAc and dorsomedial thalamus)[44, 48].

Coherently, in a functional perspective, the dopaminergic SNc and VTA show highly significant FC with core regions of the SMN and SN[66], with differentiated patterns.

The SNc was found to be more strongly connected to regions of the SMN (i.e., dorsal striatum, globus pallidus, subthalamic nucleus, sensory and motor cortices), while the VTA with regions of the SN and DMN (i.e., ventral striatum/NAc and dorsomedial thalamus, as well as ventromedial PFC, perigenual ACC, precuneus and PCC)[66-68]. Interestingly, DA receptors show a distinct distribution among RSNs, with D1 receptors being highly expressed in the motor cortical regions of the SMN, while D2-like receptors in insular and cingulate regions, as part of the SN and DMN[44].

Further confirming the chemical-functional link between DA and RSNs, PET-fMRI studies demonstrated a relationship between levels of DA receptor binding and intra-network FC of SMN, SN and DMN[69, 70].

Anatomically, the serotonergic projections of RNi involve regions of the SMN (mainly the striatum and sensorimotor cortices), and DMN (in particular the medial OFC, cingulate and temporal cortices)[51-55].

In line with anatomical data, the dorsal and central RNi were found to be functionally connected with DMN regions (e.g., PCC, precuneus, perigenual ACC and ventromedial PFC), the magnus RNi with core regions of the SN (e.g., dorsal ACC, dorsomedial thalamic nucleus and insular cortex), and the pontis RNi with regions of the SMN (e.g., putamen and SMA)[66].

Interestingly, RNi shows positive FC with basal ganglia, thalamus, ACC and insula, but negative FC with sensorimotor cortices[71].

The same study found an association between RNi FC and regional 5-HT transporter binding, better specifying the previous FC data[71].

Moreover, 5-HT receptors show a peculiar distribution among RSNs, with 5-HT1 receptors being highly expressed in sensory and motor cortical regions of the SMN[52, 56-58], while 5-HT2 receptors also expressed in DMN regions[51] .

Finally, confirming again the chemical-functional link, another PET-fMRI study demonstrated a relationship between levels of 5-HT receptor binding and networks activity (e.g., BOLD signal in the DMN)[72]. See **Figure 1**.

AIM OF THE STUDY

The aim of this work was to investigate the neurotransmitters modulation of RSNs in healthy, by reviewing the relevant work on this topic and performing complementary analyses. Such data might be integrated in a coherent model of neurotransmitters-RSNs interaction, which in turn could improve the understanding of the pathophysiology of psychiatric disorders.

We reviewed the resting-state fMRI studies on healthy subjects that investigate the relationships between DA, 5-HT and RSNs.

In order to complement the reviewed data on the connectivity patterns of neurotransmitters nuclei and effects of neurotransmitters manipulation on RSNs activity, we aimed to investigate how subcortical-cortical functional connections of DA-related substantia nigra pars compacta (SNc) and 5-HT-related raphe nuclei (RNi) (as measured by FC) may affect the activity in cortical SMN and DMN (as measured by neuronal variability).

To ensure that features identified in the analysis were not spurious or resulting from overfitting, we applied the same analysis steps to an independent dataset, which consisted of 119 HC and is part of an openly available resting-state fMRI dataset (OpenfMRI database UCLA Consortium for Neuropsychiatric Phenomics LA5c Study - CNP: https://openfmri.org/dataset/ds000030/).

In the discussion section, we proposed a working model on such neurotransmitters-RSNs relationships along with its implications for psychiatric disorders.

REVIEWED DATA

Search strategy and studies selection

The PubMed database was searched for abstracts in English language up to June 2018, using the following search terms: (serotonin, dopamine, noradrenaline) AND (resting-state networks, default-mode network, salience network, sensorimotor network, central executive network, auditory resting-state network, visual resting-state network). Reference lists of original articles were screened for additional relevant citations.

The retrieved citations were screened to select the following types of studies: case-control resting-state functional magnetic resonance imaging (fMRI) studies on healthy subjects regarding the relationships between dopamine (DA), serotonin (5-HT), noradrenaline and resting-state networks (RSNs).

A number of studies were excluded from the present work. Pharmaco-MRI studies investigating the modulation of resting-state activity by 5-HT reuptake inhibitors (SRIs) agents in healthy show conflicting results[73].

This could depend on various issues: different SRIs show intrinsic multiple effects on different neurotransmitters systems and are characterized by different pharmacodynamics; moreover, the 5-HT transporter blockade induces only indirect, variable and rather unpredictable effects on 5-HT and other neurotransmitters systems.

Accordingly, it was highlighted that SRIs' pharmacological challenge studies are not well suited to investigate the physiological effects of a specific neurotransmitter, such as the 5-HT, on functional brain activity[74]. Therefore, these studies were not included in this work.

For the same reasons, studies using methylphenidate, atomoxetine, or reboxetine[75-78] were also excluded, as they affect both the dopaminergic and noradrenergic systems at

the same time, and/or produce indirect, unspecific or variable effects on these neurotransmitter systems.

Analogously, studies that use drugs like 3,4-methylenedioxymethamphetamine (MDMA) and hallucinogens were excluded because of their widespread and multiple effects on neurotransmitter systems[79-81].

Regarding neurotransmitters, the relationship between the noradrenergic system and RSNs has been mainly investigated by means of pharmaco-MRI studies that used reboxetine or atomoxetine[77, 78, 82, 83]; only one study explored the effect of acute stress, cortisol and noradrenaline response to large-scale networks, using propranolol and metyrapone to distinguish the relative weight of the two stress markers in the reorganization of networks; however, the Authors conclude that is not possible to exclude the possibility that interactive or additive effects of noradrenaline and cortisol may occur[84]. Consequently, no works on noradrenaline were included.

Finally, with regard to RSNs, the retrieved works on central executive network (CEN) were also excluded (since they use the above-mentioned drugs, investigate the genetics polymorphisms regulating the 5-HT synthesis or the genetic variation of COMT[85-90]), while studies investigating the neurotransmitters effect on visual or auditory RSNs were not found.

Thus, the remaining studies that were included in this work concern the DA or 5-HT effects on sensorimotor network (SMN), default-mode network (DMN) and salience network (SN), in healthy[74, 91-100].

In particular, the selected studies investigate functional connectivity (FC) - using region of interest (ROI), seed-based correlation analysis and independent component analysis approaches - or fractional amplitude of low-frequency fluctuations (fALFF) or temporal variability of fMRI signal[74, 91-100].

These measures provide information on between-regions long distance correlation and regional amplitude or temporal variance in spontaneous blood oxygenation level dependent (BOLD) fluctuations, respectively.

In these studies, the administration of levodopa (L-DOPA) was used to increase the dopaminergic activity[91-94], while the administration of antipsychotics (e.g., haloperidol) and the phenylalanine/tyrosine depletion (APTD) were used to decrease the dopaminergic activity[91, 94-97].

On the other hand, the acute tryptophan depletion (ATD) was used to decrease serotonergic activity[98, 99], while platelet 5-HT uptake maximal velocity (Vmax), which is inversely related to 5-HT availability, was used to investigate the serotonergic activity (by using a mixed-effects multilevel analysis technique that tests for linear correlations between whole-brain BOLD activity and platelet 5-HT Vmax)[74].

Modulation of resting-state networks by neurotransmitters

Dopamine and resting-state networks

A role of DA in the regulation of SMN activity was demonstrated. In particular, the FC between basal ganglia and left pre- and post-central gyri/motor cortex increased after administration of levodopa (L-DOPA) and decreased after administration of haloperidol, when compared to placebo, in healthy volunteers[91]. In addition, a nonlinear (quadratic) effect of dopaminergic drug on the FC between basal ganglia and dorsal ACC and MCC was found[91].

Furthermore, a L-DOPA-related increase in motor network FC between brainstem, putamen and cerebellum was showed[92]. On the other hand, pramipexole has shown to induce no effects on the global functional architecture of SMN with a decrease in FC[100].

Interestingly, a recent work on healthy subjects demonstrated that L-DOPA

administration increases neuronal variability in various somatosensory (postcentral gyrus) and motor (precentral gyrus) regions, as well as in auditory (superior temporal gyrus) and visual (occipital cortex) areas; moreover, the extent of the L-DOPA-induced changes in variability positively correlated with the extent of FC changes across distributed cortical regions, including post/pre-central gyri, superior temporal gyrus and occipital cortices[93].

Coherently, in another recent work on healthy subjects, the decrease in DA signaling via phenylalanine/tyrosine depletion (APTD) was found to decrease FC, neuronal variability, and stability (as shown by increased entropy) of the SMN, as well as its integration within the global intrinsic activity[95].

According to these data, DA signaling seems to increase intra-network FC and activity within the SMN.

DA activity was also found to be involved in the SN modulation. In healthy volunteers, L-DOPA and haloperidol challenges increased and decreased, respectively, the FC between ventral striatum and insula[94].

Moreover, L-DOPA increased the FC between the inferior ventral striatum (i.e., NAc) and VLPFC, when compared to placebo; in turn, the L-DOPA-related increase in NAc-VLPFC FC was inversely correlated with decrease in caudate-PCC FC[92].

These findings suggested that striatal DA circuits may provide a mechanism for the active suppression of DMN under conditions that require increased processing of external stimuli with respect to associative stimuli[92].

Conversely, DA depletion via APTD in healthy adults was associated with decreased FC between ventral striatum and VLPFC during a set-switching task[96]. Coherently, in another work on healthy subjects, DA depletion via APTD also induced a decrease in FC, neuronal variability and stability of the SN, along with its integration within the

global intrinsic activity (analogously to the SMN, so that SMN and SN resulted to be the two main affected networks by DA manipulation)[95].

These data suggest that DA signaling increases intra-network FC and activity within the SN.

Finally, DA was found to modulate the DMN activity. Specifically, L-DOPA administration in healthy subjects strongly reduced the connectivity within the DMN, reducing the FC within the PCC and between PCC and medial PFC[92].

Moreover, L-DOPA was found to reduce the striatal involvement within the DMN, decreasing the FC between caudate and different DMN regions (especially PCC)[92]. On the other hand, a decrease in DA activity via ATDP in healthy adults was associated with a reduced task-related suppression of DMN activity[96], and reduction of anticorrelation between DMN and task positive networks[97].

According to these data, DA signaling seems to decrease intra-network FC and activity within the DMN.

Serotonin and resting-state networks

5-HT changes were found to affect the SMN activity. A reduction of 5-HT activity via acute tryptophan depletion (ATD) induced increases in fractional amplitude of low-frequency fluctuations (fALFF) in the superior parietal lobule, paracentral lobule and precentral gyrus in healthy subjects[98].

In another study on healthy volunteers, the platelet 5-HT uptake maximal velocity (Vmax), which is inversely related to 5-HT availability, showed a linear relationship with whole-brain BOLD signal and directly correlated with the primary motor and premotor cortices activation during emotional tasks[74].

These data suggest that 5-HT signaling reduces the SMN activity.

With regard to DMN, the increase in platelet 5-HT Vmax significantly predicted a suppression in the DMN activity, suggesting a potential effect of 5-HT in the DMN activity enhancement[74].

Coherently, the reduction of 5-HT activity via ATD was significantly associated with decreased fALFF in the PCC/precuneus and medial PFC[98]. Finally, another study detected reduced FC in the precuneus via ATD[99].

These data suggest that 5-HT signaling increases the DMN activity. See **Supplemental Table 1**.

RELATIONSHIP BETWEEN FUNCTIONAL CONNECTIONS OF NEUROTRANSMITTERS NUCLEI AND RESTING-STATE NETWORKS ACTIVITY: EMPIRICAL DATA

In order to complement the reviewed data on the connectivity patterns of neurotransmitters nuclei and effects of neurotransmitters manipulation on RSNs activity, we investigated how subcortical-cortical functional connections of DA-related SNc and 5-HT-related RNi (as measured by FC) affect the activity in cortical SMN and DMN (as measured by neuronal variability), in two independent datasets of healthy subjects.

We found a positive correlation of SNc-basal ganglia FC with neuronal variability in the SMN. This complements the reviewed data on the facilitating effect of DA signaling on SMN and psychomotor activity.

Conversely, we found a negative correlation of RNi-SMN FC with neuronal variability in the SMN and in SMN/DMN ratio (reflecting a shift of the networks balance toward the DMN).

This complements the reviewed data on the inhibitory and facilitating effects of 5-HT signaling on SMN and DMN respectively, along with inhibitory effects on psychomotor activity and impulsivity.

Considering the reviewed data, our empirical results suggest that manipulation of neurotransmitters signaling affects the subcortical-cortical functional connections of neurotransmitters nuclei, which in turn modulate the cortical activity of RSNs. See **Figure 2**.

Methods

Participants and clinical assessment

Participants were recruited from the Genoa metropolitan area (Italy). The study has been conducted on 106 healthy controls (HC).

The Ethics Committee of San Martino Policlinic Hospital of Genoa approved the study, and written informed consent was obtained from all participants.

Inclusion criteria were as follows: age between 18 and 60 and ability to provide written informed consent.

Exclusion criteria were as follows: psychiatric disorders; neurological diseases (stroke, cerebral vascular malformations, or epilepsy); previous head injury with loss of consciousness (for 5 or more minutes); severe or decompensated somatic diseases; current alcohol and substance abuse (during the preceding 3 months), history of alcohol or substance dependence, history of abuse of synthetic or new drugs; pregnancy and lactation; left-handedness; the inability to undergo an MRI examination (claustrophobia, metal implants, and so forth); history of treatment with chemotherapy or brain radiotherapy.

fMRI data acquisition

Images were acquired using a 1.5-T GE scanner with a standard head coil. Foam pads were used to reduce head motion and scanner noise.

fMRI scanning was carried out in the dark, with participants instructed to keep their eyes closed, to relax, and to move as little as possible.

Functional images were collected by using a gradient Echo Planar Imaging (EPI) sequence sensitive to BOLD contrast (TR/TE = 2,000/30 ms, flip angle = 90°, FOV = 24 cm). Whole-brain volumes were acquired in 33 contiguous 4-mm-thick transverse slices, with a 1-mm gap and 3.75×3.75-mm^2 in-plane resolution.

For each participant, fMRI scanning lasted 5 min and acquired a total of 150 scans.

In addition, 3D T1-weighted anatomical images were acquired for all participants in a sagittal orientation by means of a 3D-SPGR sequence (TR/TE = 11.5/5 ms, IR = 500 ms, flip angle = 8°, FOV = 25.6 cm) with an in-plane resolution of 256×256, and slice thickness of 1 mm.

Data processing

RS fMRI data were preprocessed and analyzed using tools from the FMRIB software library (FSL 5.0, http://www.fmrib.ox.ac.uk/fsl/)[101].

The preprocessing included: (1) slice timing correction; (2) volume realignment; (3) brain extraction; (4) regression out of linear and non-linear drift, head motion and its temporal derivative, and mean time-series from the white matter and cerebrospinal fluid to control for non-neural noise[14, 102]; (5) non-linear alignment and normalization of anatomical and functional images with the FSL MNI152 2mm T1 standard space template; (6) spatial smoothing with a 6mm full-width at half-maximum isotropic Gaussian kernel.

The data were filtered within the standard frequency band of 0.01–0.08Hz, which is thought to reflect mainly neuronal fluctuations, and is less affected by physiological variables like respiration and aliased cardiac signals that fall in the other frequency ranges[5, 6, 34, 103, 104].

Head motion can affect resting-state measures. Therefore, in addition to regression out of temporal derivatives related to head motion (along with white matter/cerebrospinal fluid signals regression and frequency band filtering for denoising), we also sought to minimize this effect in several other ways[105-107]. The motion parameters from the volume realignment step were used to exclude participants using a strict threshold of translations greater than 2mm or rotations greater than 2° in each direction.

Moreover, motion scrubbing (or frame censoring) has been applied to our data. In particular, the FSL motion outlier tool was used to identify individual volumes that may be influenced by excessive movement (using an intensity difference metric thresholded at the 75th percentile + 1.5 times the interquartile range). These volumes plus the ones immediately before and after them were excluded from the FC calculation. Finally, mean head motion was entered as covariate in all the subsequent correlation analyses.

Data analyses

FC of SNc and RNi, as well as neuronal variability (SD) of SMN and DMN, was calculated, and their relationship was investigated.

In particular, we first calculated the FC of SNc and RNi with pallidum (as a measure of SNc/RNi-related subcortical FC), by using a ROI-to-ROI approach. Bilateral SNc and RNi masks from the ATAG-Atlas (http://www.nitrc.org/projects/atag)[108], as well as a bilateral pallidum mask from the Harvard-Oxford subcortical atlas, were used as ROIs. The seed reference time-series of each ROI was obtained by averaging the fMRI time-series of all voxels within.

Pearson's correlation coefficient was calculated between the two ROI timecourses and transformed to z-value by means of the Fisher r-to-z transformation, in order to improve normality.

We then calculated the FC of SNc and RNi with SMN and DMN (as a measure of SNc/RNi-related cortical FC) by using the same approach and methodology as above. Bilateral SNc and RNi masks from the ATAG-Atlas, as well as a bilateral mask of the cortical SMN and DMN as defined by Yeo et. al[109], were used as ROIs.

Secondly, the SD - operationalized as standard deviation of the amplitude of resting-state BOLD signal, which represent an indirect proxy of neuronal activity[17] - was

calculated in the whole brain and then extracted from the cortical masks of SMN and DMN as defined by Yeo et. al[109].

Statistical analyses

In order to test the potential correlation between SNc- or RNi-related FC and SD in cortical SMN or DMN, such measures were entered in partial correlation analyses (with age, gender and motion as covariates).

In particular, we calculated the correlation of SNc-pallidum FC, SNc-SMN FC, and SNc-DMN FC with SMN SD, DMN SD and SD in the SMN/DMN ratio.

Then we calculated the Spearman partial correlation (with age, gender and motion as covariates) of RNi-pallidum FC, RNi-SMN FC, and RNi-DMN FC with SMN SD, DMN SD and SD in the SMN/DMN ratio.

The results were thresholded at a Bonferroni corrected $p<0.05$ (18 correlation analyses, Bonferroni-corrected $p\leq0.002$). Statistical analyses were performed in SPSS version 23.

Finally, to further confirm the specificity of our findings, the FC measures that were found to be significantly correlated with SD measures in the previous analysis were entered in a whole brain voxel-wise regression analysis with SD maps (with age, gender and motion as covariates). A $p<0.05$, corrected for family-wise error using the threshold-free cluster enhancement (TFCE), was set[110].

Results

In our main dataset, in the correlation analysis, a significant positive correlation was found between SNc-pallidum FC and SMN SD ($\rho=0.298$, $p=0.002$).

By contrast, a significant negative correlation of RNi-SMN FC with both SMN SD ($\rho=-0.303$, $p=0.002$) and SMN/DMN SD ($\rho=-0.324$, $p=0.001$) was found. No other significant results were detected.

SNc-pallidum FC and RNi-SMN FC were then entered in a regression analysis with SD map. Confirming and specifying the previous results, SNc-pallidum FC was significantly and positively related to SD in the sensorimotor cortical regions.

By contrast, RNi was significantly and negatively related to SD in cortical regions of the SMN (see **Figure 2**).

Replication study

Methods

For each participant, images were acquired by using a 3T scanner. Functional images were collected by using a gradient 5 min length Echo Planar Imaging (EPI) sequence sensitive to BOLD contrast (TR/TE= 2,000/30 ms). 3D T1-weighted anatomical images (TR/TE= 2.53/0.331 ms) were also collected. For more detailed information, see the website.

We applied to these data the same steps for preprocessing, ROI-to-ROI FC and SD calculation (using the same masks), as well as their correlation calculation and whole brain regression analysis, as in our main dataset (see above).

In order to replicate the significant results obtained in our main dataset, we calculated the correlation between SNc-pallidum FC and SMN SD as well as the correlation of RNi-SMN FC with SMN SD and SMN/DMN SD (with age, gender and motion as covariates).

Finally, the same FC measures were entered in a whole brain regression analysis with SD map (with age, gender and motion as covariates).

Results

In the replication dataset, as in our main dataset, in the correlation analysis, SNc-pallidum FC was significantly positively correlated with SMN SD (ρ=0.225, p=0.015), while RNi-SMN FC was significantly negatively correlated with both SMN SD (ρ=-0.186, p=0.045) and SMN/DMN SD (ρ=-0.216, p=0.020).

Moreover, as in our main dataset, the whole brain voxel-wise regression analysis revealed a significant positive relationship between SNc-pallidum FC and SD in the sensorimotor cortical regions, while a significant negative relationship between RNi-SMN FC and SD in the SMN (see **Figure 2**).

Discussion of the empirical and replicated data

The main findings of the study were as follows. Healthy subjects in both datasets showed: (1) a positive linear correlation between SNc-pallidum FC and SMN SD; (2) a negative linear correlation of RNi-SMN FC with SMN SD and SMN/DMN SD; (3) a significant positive relationship between SNc-pallidum FC and SD in the sensorimotor regions; (4) a significant negative relationship between RNi-SMN FC and SD in the SMN.

According to these findings, subcortical-cortical FC of brainstem neurotransmitters nuclei and cortical SD at a network level are consistently related.

Thus, the increase in FC between the DA-related SNc and basal ganglia is associated with increase in SD in the SMN.

By contrast, the increase in FC between the 5-HT-related RNi and SMN cortex is associated with a decrease in SD in the SMN and a tilting of networks balance toward the DMN SD.

Our empirical results complement the reviewed data, suggesting that changes in the functional connections of brainstem neurotransmitter nuclei (e.g., by manipulation of

neurotransmitters activity) may induce a subcortical-cortical functional re-organization that alters the baseline intrinsic activity of cortical networks and their balances. Moreover, such changes are neurotransmitters nuclei and networks specific. Accordingly, functional connections of DA-related SNc may favor a predominance of SMN activity, while functional connections of 5-HT-related RNi may favor a tilting of networks balance toward the DMN activity.

CONCLUSIONS

According to the reviewed and empirical data, neurotransmitters signaling impacts the functional configuration (i.e., FC) and activity (i.e., fALFF/neuronal variability) of RSNs.

Dopaminergic SNc-nigrostriatal pathway is mainly connected with SMN and VTA-related mesocorticolimbic pathway with SN, while serotonergic RNi-related pathways are connected with SMN and DMN.

SNc-related FC is positively correlated with SMN activity, while RNi-related FC is negatively correlated with SMN activity (tilting the networks balance toward the DMN). DA signaling is associated with increase in FC and activity in SMN and SN, while 5-HT signaling is associated with decreased SMN and increased DMN activity.

Impact of neurotransmitters on resting-state networks

FC measures the coherence of BOLD signal oscillations across different brain areas[111]. The exact mechanism underlying FC is still debated, and several hypotheses regarding its physiological meaning have been provided.

It has been supposed that FC allows to probe cyclic modulation of long distance neuronal synchronization of low-frequency oscillations[33, 34, 111-113].

Moreover, several investigations suggest that FC is most likely phase-based, and FC has been proposed to emerge as a consequence of the lag structure of brain's intrinsic activity, thus assuming its dynamic origin[114, 115].

Such correlation of low-frequency fluctuations between various subcortical and cortical regions consistently differentiates distinct large-scale networks in the functional architecture of intrinsic brain activity[33, 34, 111, 113].

Thus, changes in FC may affect the communication pattern between different neuronal areas within or between networks, and have been shown to correlate with behavioral measures[111].

On the other hand, fALFF and temporal variability of BOLD signal can be considered as indexes of ongoing intrinsic neuronal activity[116-123]. Changes in such amplitude and variability in resting-state activity can affect the subsequent neuronal processing of incoming stimuli and neuronal outputs, being central to behavioral performance[116-123].

The relationship between FC and fALFF/temporal variability of BOLD signal is complex and still poorly investigated. In general, a positive correlation between such measures in healthy has been found[93, 95, 124, 125].

However, this relationship may be different in distinct brain areas and differentially modulated by distinct neurotransmitter systems, in relation to anatomical and chemical factors such as specific neuronal circuitry or receptors type and distribution – see our empirical data on the opposite correlation of neuronal variability in the SMN with FC of SNc (positive) or RNi (negative).

The reviewed data show that activity changes in a specific neurotransmitter system differentially modify FC and fALFF/variability (along with their relationship) in specific RSNs.

Accordingly, we hypothesize that the activity of neurotransmitters-related brainstem nuclei modulates the synchronization pattern of resting-state low-frequency oscillations (as measured by FC) in the different subcortical and cortical regions of RSNs.

In turn, changes in neuronal synchronization between network regions may affect the basal level of ongoing intrinsic neuronal activity (as measured by fALFF or neuronal variability) of such RSNs, resulting in changes of input/output processing, and finally leading to specific and different psychological/behavioral patterns.

Accordingly, considering the reviewed work and our empirical data, we assume that DA signaling synchronizes and thus increases the activity of SMN (as mediated by functional connections of the SNc-related nigrostriatal pathway) and SN (as mediated by functional connections of the VTA-related mesocorticolimbic pathway), while reducing the DMN activity.

This may favor a behavioral pattern characterized by psychomotor activation and salience to sensory stimuli.

Conversely, we assume that 5-HT signaling modulates the synchronization pattern and thus reduces the activity of SMN (as mediated by functional connections of the RNi-related pathways), tilting the networks balance towards the DMN.

This may favor a behavioral pattern characterized by psychomotor inhibition and predominance of internal thought.

In sum, DA and 5-HT signaling may respectively favor the predominance of SMN-SN or DMN activity and related behavioral patterns. See **Figure 3**.

IMPLICATIONS FOR MAJOR PSYCHIATRIC DISORDERS

BD is defined by the occurrence of distinct psychopathological states with opposing symptomatology. Mania is characterized by excited psychomotor behavior (e.g., hyperactivity/impulsivity) and affectivity (e.g., euphoria/irritability) along with externally-focused thought (e.g., distractibility/flight of ideas)[126, 127]. Conversely, depression (in its typical inhibited form) is characterized by inhibited psychomotor behavior (e.g., poor motricity/motor retardation) and affectivity (e.g., depressed mood/anhedonia) along with internally-focused thought (e.g., excessive self-focusing/ruminations)[126, 127].

Accordingly, in our previous work, we detected opposing alterations in cortical RSNs in such distinct phases of illness[17, 124, 128, 129].

Specifically, a predominance of SMN occurs in mania, as shown by tilting of the balance between neuronal variability in SMN and DMN toward the SMN at the expense of DMN[17], along with greater global signal representation in SMN areas[129] and reduced connectivity within the DMN[124, 128].

Finally, a decrease in regional homogeneity and degree of centrality (measures of local and global connectivity, respectively) in slow4 were detected in the DMN (moreover, the deficit of faster frequencies in the DMN was associated with their increase in SMN areas) [130].

Interestingly, psychomotor hyperactivity positively correlated with SMN connectivity, while distractability (which can be considered a deficit in thought) negatively correlated with DMN connectivity[130].

Conversely, a predominance of DMN occurs in depression, as suggested by tilting in SMN/DMN balance toward the DMN at the expense of SMN[17], by decreased amplitude of low-frequency fluctuations found in SMN areas, by increased representation of

global signal in DMN areas[131] and by an increase in regional homogeneity in DMN regions[130].

Such opposing alterations in the functional architecture of resting-state activity were related with manic and depressive symptomatology, respectively, further supporting the link between changes in intrinsic brain activity and psychopathology[17, 124, 128, 129].

On the other hand, a core feature of schizophrenia is psychotic symptomatology, including delusions and hallucinations (which nevertheless also occur in other disorders, such as BD).

However, psychopathological alterations in schizophrenia are heterogeneous, since psychosis includes a wide range of patterns (from excessive salience attribution to irrelevant incoming sensory stimuli, up to dreaming states dissociated from the environment), and is often associated with negative and cognitive symptoms, in different combinations[126, 127].

Therefore, schizophrenia has been associated to heterogeneous alterations in resting-state activity, including increased coupling/activity in SN, SMN and sensory networks, along with disconnection/reduced activity in DMN (mainly in unmedicated patients)[22, 132-134], but also increased coupling/activity in DMN with reduced activity in SN, SMN and sensory networks[20, 21, 43, 135-137].

Independently, various changes in DA and 5-HT neurotransmitter systems have been documented in the pathophysiology of affective disorders and schizophrenia[25-27, 29, 138, 139]. In particular, decreased 5-HT transmission overall (and especially in the manic phase) and decreased DA transmission in the depressive phase resulted to be the most consistent neurotransmitter findings in BD[140, 141].

Conversely, increased DA transmission (with alterations in DA release and synthesis capacity) is consistently detected in schizophrenia, in particular during psychotic states

(interestingly, increased DA signaling seems to also occur in psychotic mania, but not in non-psychotic mania)[24, 25, 32, 138, 140, 141].

The impact of dopaminergic or serotonergic changes on neural activity in related circuitry and networks in such psychiatric disorders is still an open issue, and data on this topic are still sparse (e.g.,[31, 142]). However, in our previous work on first-episode and drug-naïve schizophrenic patients, we detected an alteration in functional connections of DA-related SNc, which was associated with an abnormal subcortical-cortical FC within the SMN[139], supporting a link between activity alterations in neurotransmitters nuclei and functional re-organization at network level.

Thus, considering these data in the context of our working model on the neurotransmitters-RSNs interaction, we hypothesize that alterations in neurotransmitters signaling result in a subcortical-cortical functional reorganization, which leads to RSNs disbalancing, finally manifesting in distinct psychopathological states.

In particular, a deficit in 5-HT signaling and/or functional disconnection of RNi may result in DMN deficit with relative predominance of SMN-SN activity, manifesting in psychomotor excitation, excessive salience to sensory stimuli and externally-focused thought, i.e., manic state[17, 124, 128, 129].

Conversely, a deficit in DA signaling and/or functional disconnection of SNc-VTA may result in SMN-SN deficit with relative predominance of DMN activity, manifesting in psychomotor inhibition, reduced salience to stimuli and internally-focused thought, i.e., depressive state[17].

Finally, a hyperactive DA signaling may result in over-activity of SMN-SN, manifesting in excessive salience attribution to irrelevant stimuli, perceptual distortions, psychomotor agitation, and thought disturbances, i.e., psychotic state.

Beyond these patterns, however, we suppose that combinations of neurotransmitters alterations (including changes in other modulators like acetylcholine or endogenous

opioids[143, 144]) may result in different RSNs alterations, thus manifesting in other complex and specific psychopathological states, including mixed states and different psychotic states (e.g., dreaming-like or dissociative states), which all can occur in various associations in BD and schizophrenia. See **Figure 4**.

Interestingly, this model is also in accordance with the relationship between spatiotemporal alterations of resting-state activity and spatiotemporal organization of psychopathological symptoms, as described in "Spatiotemporal psychopathology"[19, 145-147].

In this framework, a three-dimensional model of brain functioning has been hypothesized [148].

An external unit, represented by the thalamus-SMN loop and the SNc-related DA signaling, is directly connected with the external environment and sets the processing of exteroceptive inputs and somatomotor outputs, thus underlying the psychomotor dimension; an internal unit, represented by the thalamus-SN loop and the VTA-related DA signaling, is directly connected to the internal/body environment and sets the processing of interoceptive inputs and visceromotor outputs, thus underlying the affective dimension; finally, an associative unit, represented by intrinsic activity of the DMN and by the RNi-related 5HT signaling, is connected with both the external and internal/body environment and sets the processing of associative inputs/outputs, thus underlying the thought dimension [148].

These units of intrinsic brain activity can couple in different combinations; the reciprocal interaction and combination between changes in the different neurotransmitter signaling, by differentially modulating the subcortical-cortical loops, may favor different balancing or coupling between the various networks, thus organizing distinct functional brain states and this can be applied, for example, to the

psychopathological states of BD, as described by Kraepelin in his model of manic-depressive illness [148].

Alterations in the neurotransmitter signaling can lead to phasic, and often recurrent, reconfigurations of intrinsic brain activity, from abnormal cortical-subcortical coupling to changes in network activity [149]. The resulting disbalance between networks, such as SMN, SN and DMN, clinically manifest in combined alterations of psychomotricity, affectivity, and thought during the manic and depressive phases of BD [149].

From a pathophysiological point of view, these alterations in the neurotransmitter signaling in BD could be the result of a damage of the limbic network mediated by an immune/inflammatory-mediated alteration of white matter [149].

In conclusion, the suggested model on neurotransmitters-RSNs interaction provides novel testable hypotheses in both humans and animal models to better understand the various resting-state changes observed in psychiatric disorders like BD and schizophrenia. This may carry not only scientific relevant but major therapeutic ramifications for the development of more targeted drugs.

FIGURES

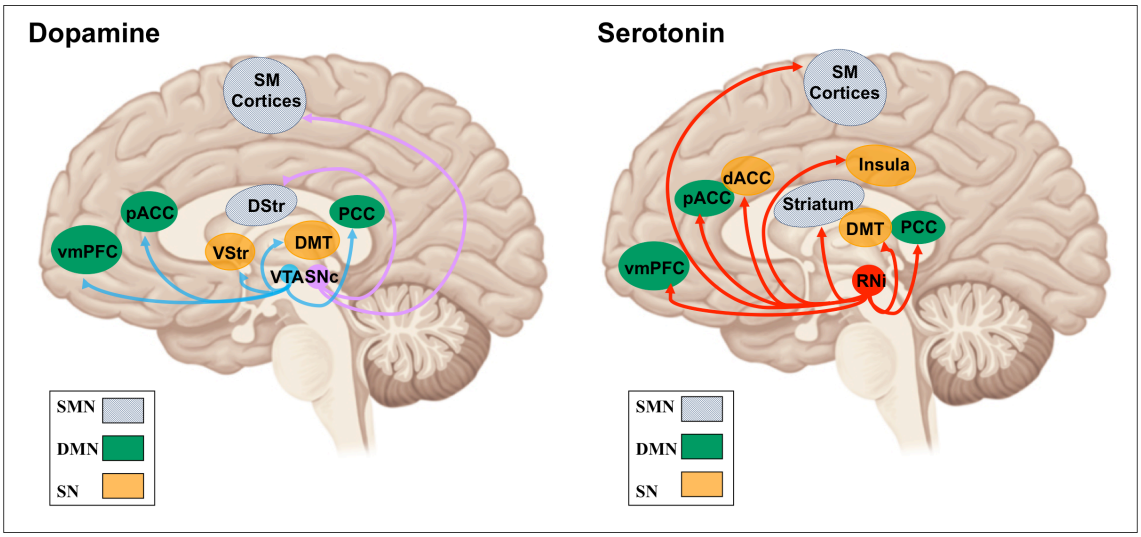
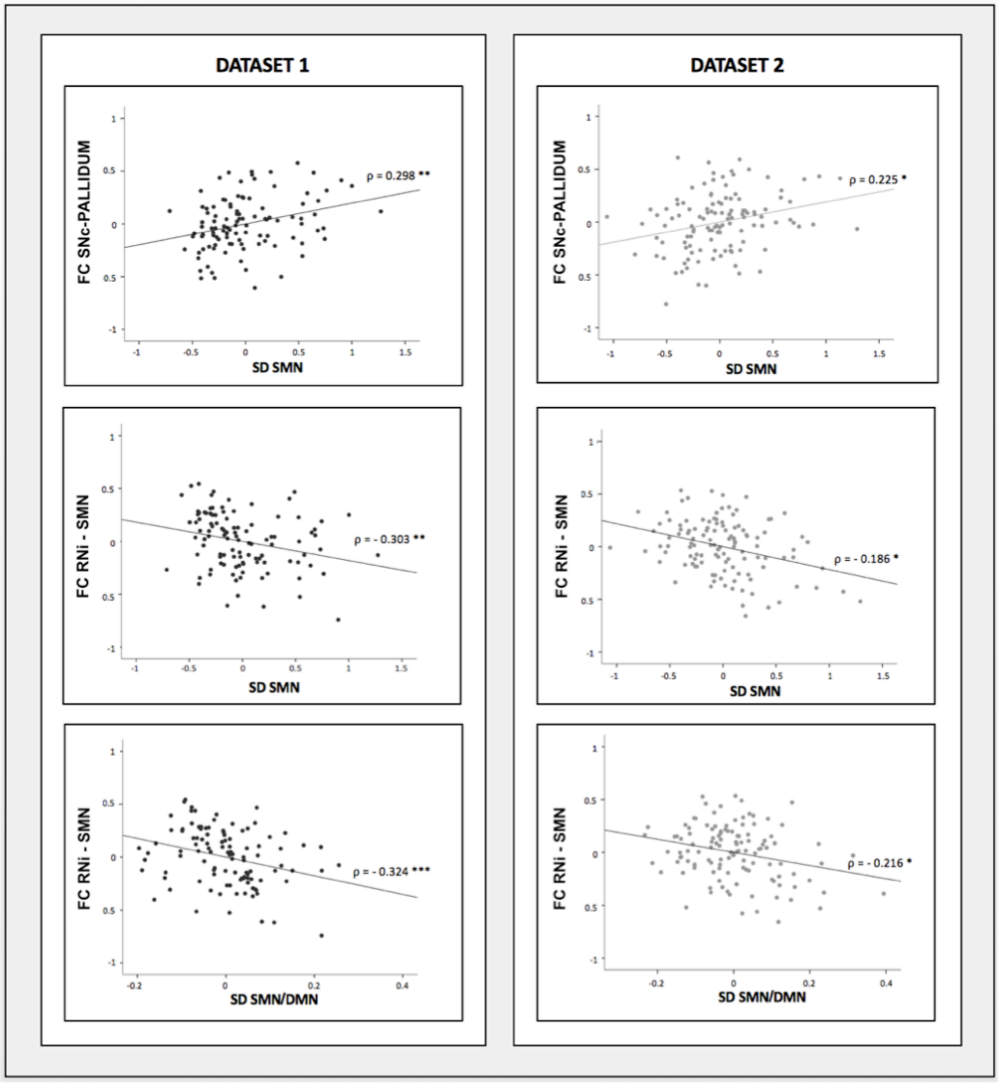


Figure 1. Neurotransmitters nuclei projections and resting-state networks

Dopamine. Dopaminergic pathways and RSNs: the nigrostriatal pathway projects mainly to core regions of the SMN, while the mesocorticolimbic pathway to the SN. **Serotonin.** Serotonergic pathways and RSNs: the main projections of the RNi involve regions of the SMN and DMN.

Abbreviations: SNc, substantia nigra pars compacta; VTA, ventral tegmental area; DStr, dorsal striatum; VStr, ventral striatum; DMT, dorsomedial thalamus; pACC, perigenual anterior cingulate cortex; PCC, posterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; SM, sensorimotor; RNi, raphe nuclei; dACC, dorsal anterior cingulate cortex; RSNs, resting-state networks; SMN, sensorimotor network; DMN, default-mode network; SN, salience network.

A


DATASET 1
DATASET 2
FC SNc-PALLIDUM
SD SMN
ρ = 0.298 **
ρ = 0.225 *
FC RNi - SMN
ρ = - 0.303 **
ρ = - 0.186 *
SD SMN/DMN
ρ = - 0.324 ***
ρ = - 0.216 *

B

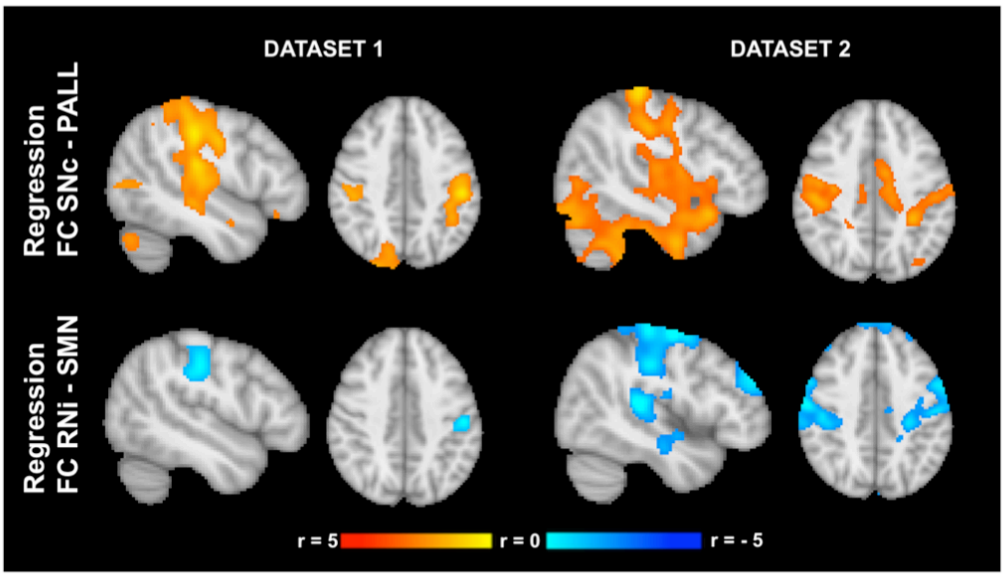

DATASET 1
DATASET 2
Regression FC SNc - PALL
Regression FC RNi - SMN
r = 5
r = 0
r = - 5

Figure 2. Relationship between functional connections of neurotransmitters nuclei and resting-state networks activity

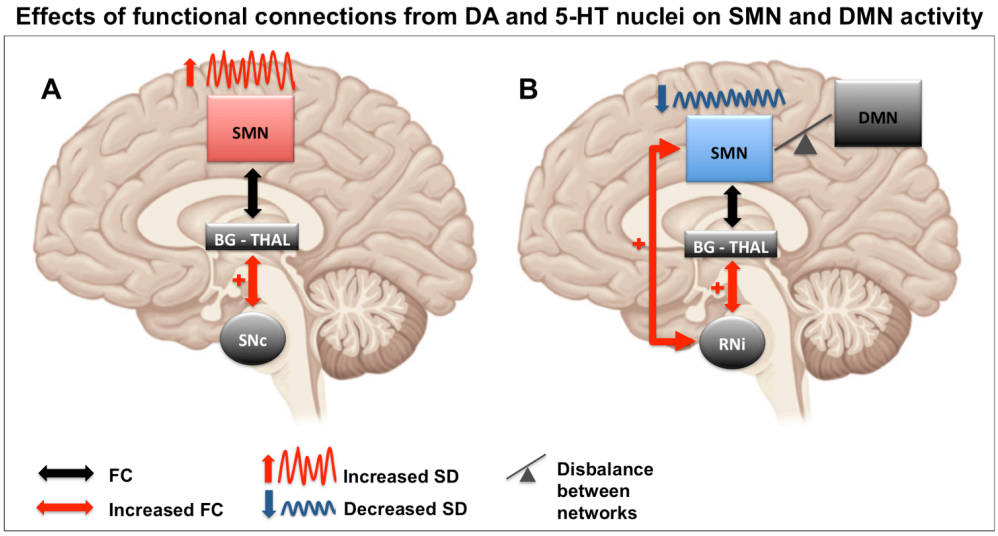
A. Correlation of SNc- or RNi-related FC with SD in cortical SMN and DMN

In both datasets of healthy subjects, a significant positive correlation was found between SNc-pallidum FC and SMN SD, while a significant negative correlation was found between RNi-SMN FC and SMN SD or SMN/DMN SD.

B. Correlations of SNc-pallidum FC and RNi-SMN FC with voxel-wise SD map

Whole brain voxel-wise regression analysis of SNc-pallidum FC and RNi-SMN FC with SD map (with age, gender and motion as covariates), showing clusters with significant correlations of SNc-pallidum FC and RNi-SMN FC with SD. A $p<0.05$, corrected for family-wise error using the threshold-free cluster enhancement (TFCE), was set. The color bar represents voxel-wise r-values. Positive relationships are shown in red-yellow, while negative relationships in blue-light blue.

Abbreviations: SNc, substantia nigra pars compacta; RNi, raphe nuclei; PALL, pallidum; SMN, sensorimotor network; DMN, default-mode network; FC, functional connectivity; SD, neuronal variability.



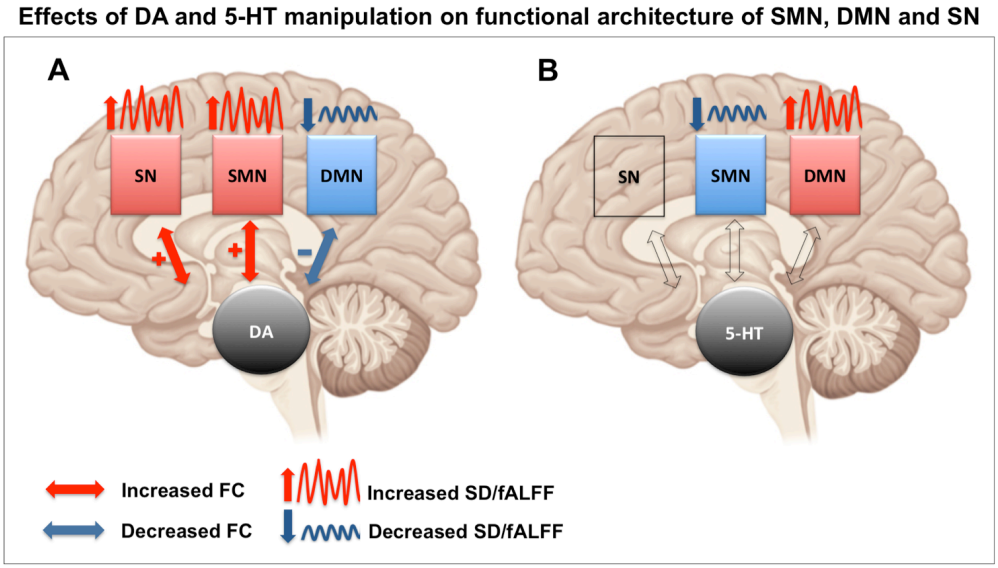


Figure 3. Summary of the empirical and reviewed data

Effects of functional connections from DA and 5-HT nuclei on SMN and DMN activity: empirical data A. Positive correlation between SNc-related FC and SMN activity. ***B.*** Negative correlation between RNi-related FC and SMN activity along with tilting of networks balance toward the DMN.

Effects of DA and 5-HT manipulation on functional architecture of SMN, DMN, and SN: reviewed data A. DA signaling is associated with an increase in FC and activity in SMN and SN, along with a decrease in FC and activity in DMN. ***B.*** 5-HT signaling is associated with a decrease in SMN activity along with an increase in DMN activity.

Abbreviations: SNc, substantia nigra pars compacta; RNi, raphe nuclei; BG, basal ganglia; THAL, thalamus; SMN, sensorimotor network; DMN, default-mode network; SN, salience network; FC functional connectivity; SD, neuronal variability; fALFF, fractional amplitude of low-frequency fluctuations; DA, dopamine; 5-HT, serotonin.

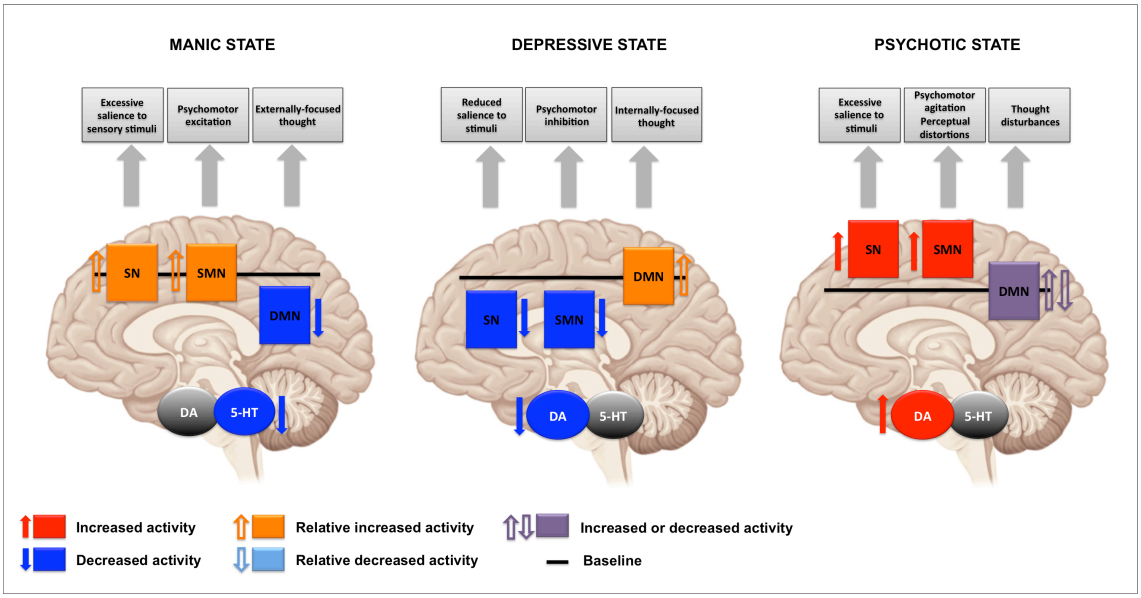
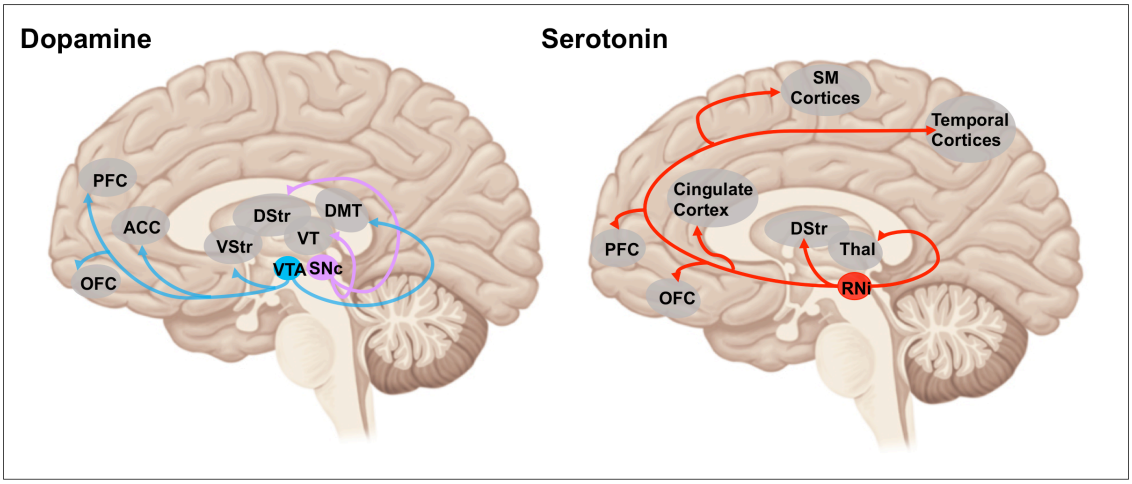


Figure 4. Hypothesis on the functional reorganization and resting-state networks disbalancing mediated by alterations in neurotransmitters signaling in different psychopathological states

Neurotransmitters signaling affects the functional architecture and balances of resting-state networks. Thus, we hypothesize that: deficit in 5-HT signaling may result in DMN deficit with relative predominance of SMN-SN activity, manifesting in the manic state; deficit in DA signaling may result in SMN-SN deficit with relative predominance of DMN activity, manifesting in the depressive state; and hyperactive DA signaling may result in over-activity of SMN-SN, manifesting in a psychotic state.

Abbreviations: SMN, sensorimotor network; DMN, default-mode network; SN, salience network; DA, dopamine; 5-HT, serotonin.

SUPPLEMENTAL FIGURE



Supplemental Figure 1. Dopaminergic and serotonergic pathways

Dopamine. Mesocorticolimbic pathway from VTA and nigrostriatal pathway from SNC. **Serotonin.** Serotonergic pathway from RNi.

Abbreviations: SNc, substantia nigra pars compacta; VTA, ventral tegmental area; DStr, dorsal striatum; VStr, ventral striatum; DMT, dorsomedial thalamus; VT, ventral thalamus; ACC, anterior cingulate cortex; PFC, prefrontal cortex; OFC, orbitofrontal cortex; RNi, raphe nuclei; Thal, thalamus; SM, sensorimotor.

SUPPLEMENTAL TABLE

Supplemental Table 1. Reviewed studies on the effects of neurotransmitters manipulation on resting-state networks

	Method	NTs	Results	Effects on RSNs
Cole et. al, Neuroimage 2013	RS fMRI after L-DOPA	↑ DA	↑ FC BG-pre/postcentral gyri	↑ SMN
			↑ FC BG-ACC/MCC after L-DOPA	↑ SMN
			↑ FC Brainstem-Putamen-Cerebellum	↑ SMN
	RS fMRI after Haloperidol	↓ DA	↓ FC BG-pre/postcentral gyri	↓ SMN
Kelly et al., J Neurosci 2009	RS fMRI after L-DOPA	↑ DA	↑ FC between brainstem, putamen and cerebellum	↑ SMN
			↑ FC NAc-left VLPFC	↑ SN
			↓ FC within PCC and ↓ FC PCC-medial PFC	↓ DMN
			↓ FC caudate-PCC	↓ FC DMN-SMN
Alavash et al., bioRxiv 2017	RS fMRI after L-DOPA	↑ DA	↑ neuronal variability in postcentral and precentral gyri	↑ SMN
			↑neuronal variability in superior temporal gyrus	↑ Auditory Net.
			↑ neuronal variability in occipital cortex	↑ Visual Net.
Cole et al., Cereb Cort 2013	RS fMRI after L-DOPA	↑ DA	↑ FC ventral striatum-insula	↑ SN

	RS fMRI after Haloperidol	↓ DA	↓ FC ventral striatum-insula	↓ SN
Nagano-Saito et al., J Neurosci 2008	task fMRI after APTD	↓ DA	↓ FC Nac-bilateral VLPFC	↓ SN
			↓ task-related suppression of DMN	↑ DMN
Carbonell et al., Neuropharm 2014	RS fMRI after APTD	↓ DA	↓ anticorrelation DMN-task positive networks	↑ DMN
Shafiei et al., Cereb Cort 2018	RS fMRI after APTD	↓ DA	↓ FC, neuronal variability, and stability (↑ entropy) in SMN and SN	↓ SMN and SN
Kunisato et al., Neurosci Res 2011	RS fMRI ATD	↓ 5-HT	↑ fALFF in superior parietal and paracentral lobule and precentral gyrus	↑ SMN
			↓ fALFF in PCC/precuneus and medial PFC	↓ DMN
Scharinger et al., PLoS One 2014	correlations between whole-brain BOLD activity and platelet 5-HT uptake Vmax	↓ 5-HT	direct correlation between ↑ platelet 5-HT uptake and ↑ BOLD in primary motor and premotor cortices	↑ SMN
			direct correlation between ↑ platelet 5-HT uptake and ↓ BOLD in DMN regions	↓ DMN
Helmbold et al., Am Aci 2016	RS fMRI ATD	↓ 5-HT	↓ FC in precuneus	↓ DMN

Abbreviations. NTs, neurotransmitters; DA, dopamine; 5-HT, serotonin; RSNs, resting-state networks; SN, salience network; SMN, sensorimotor network; DMN, default-mode network; Net, network; RS, resting-state; fMRI, functional magnetic resonance imaging; FC, functional connectivity; fALFF, fractional amplitude of low-frequency fluctuation; BOLD, Blood Oxygenation Level Dependent; APTD, phenylalanine/tyrosine depletion; ATD, acute tryptophan depletion; BG, basal ganglia; NAc, nucleus accumbens; ACC, anterior cingulate cortex; MCC, middle cingulate cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.

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